PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

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Date of mailing *(day/month/year)*	
08 September 2006 (08.09.2006)	
Applicant's or agent's file reference M/44142-PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2004/010939	International filing date *(day/month/year)* 30 September 2004 (30.09.2004)
Applicant BASF AKTIENGESELLSCHAFT et al	

1. **Transmittal of the translation to the applicant.**

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

KR

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Agnes Wittmann-Regis

TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
M/44142-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/010939	30.09.2004	01.10.2003
International Patent Classification (IPC) or national classification and IPC		
c07d333/16		
Applicant		
BASF AKTIENGESELLSCHAFT		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-50 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-26 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/8-8/8 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☒ complied with.

   ☐ not complied with for the following reasons:

The different inventions are as follows:

Claims 1-4 and 6
Non-enzymatic methods for producing 3-methylamino-1-(thien-2-yl)-propanol-1.

Claims 5 and 7-26
Enzymatic methods for producing 3-methylamino-1-(thien-2-yl)-propanol-1, as well as enzymes for carrying out said methods, nucleic acid sequences that code for those enzymes, expression cassettes containing them, and vectors and recombinant hosts.

For the following reasons, these inventions are not so linked as to form a single general inventive concept (PCT Rule 13.1):

A method for producing compounds of formula I is already known. Therefore, the problem to be solved by the present invention can be regarded as that of providing new, and possibly improved, methods. The problem is solved in claims 1-4 using a non-enzymatic method. In claims 5-26, the problem is solved using an enzymatic method, and the enzymes needed to carry out this method, the nucleic acid sequences that code for these enzymes, the expression cassettes that contain them, and vectors and recombinant hosts are claimed. There is no technical relationship between these two solutions.

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-26	YES
	Claims		NO
Inventive step (IS)	Claims	1-26	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

V.1 The present invention relates to a method for producing 3-methylamino-1-(thien-2-yl)-propanol 1.

V.2 This report makes reference to the following documents:

D1: PATENT ABSTRACTS OF JAPAN Vol. 2003, No. 11, 5 November 2003 (2003-11-05) & JP 2003 192681 A (MITSUBISHI RAYON CO LTD), 9 July 2003 (2003-07-09)

D2: WHEELER W J ET AL: "AN ASYMMETRIC SYNTHESIS OF DULOXETINE HYDROCHLORIDE, A MIXED UPTAKE INHIBITOR FOR SEROTONIN AND NOREPHINEPHRINE, AND IST C-14 LABELED ISOTOPOMERS" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, SUSSEX, GB, Vol. 36, No. 3, 1995, pages 213-224, XP009019756 ISSN: 0362-4803, mentioned in the application

D3: KAMAL A ET AL: "Chemoenzymatic synthesis of duloxetine and ist

enantiomer: lipase-catalyzed resolution of 3-hydroxy-3-(2-thienyl) propanenitrile" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, Vol. 44, No. 25, 16 June 2003 (2003-06-16), pages 4783 4787, XP004426893 ISSN: 0040-4039, mentioned in the application

D4: LIU H ET AL: "CHEMO-ENZYMATIC SYNTHESIS OF THE ANTIDEPRESSANT DULOXETINE AND IST ENANTIOMER" CHIRALITY, WILEY-LISS, NEW YORK, US, Vol. 12, No. 1 , 2000, pages 26-29, XP009000316 ISSN: 0899-0042, mentioned in the application

D5: DE 102 48 479 A (CONSORTIUM ELEKTROCHEM IND) 6 May 2004 (2004-05-06)

D6: DE 102 48 480 A (CONSORTIUM ELEKTROCHEM IND) 6 May 2004 (2004-05-06)

Documents D5 and D6 were published after the priority date and are therefore not regarded as prior art.

D7: HUMMEL W: "NEW ALCOHOL DEHYDROGENASES FOR THE SYNTHESIS OF CHIRAL COMPOUNDS" ADVANCES IN BIOCHEMICAL ENGINEERING, BIOTECHNOLOGY, SPRINGER, BERLIN, DE, Vol. 58, 1997, pages 145-184, XP000677754 ISSN: 0724-6145

D8: DATABASE EMBL [Online] 14 February 2003 (2003-02-14), "Lactobacillus brevis radh gene for R-specific alcohol

dehydrogenase" XP002339858 Database accession no. AJ544275

D9: DATABASE EMBL [Online] 9 August 2001 (2001-08-09), "Sequence 7 from patent US 6225099." XP002339860 Database accession no. AR148418

D10: DATABASE Geneseq [Online] 31 August 2001 (2001-08-31), "DNA encoding Candida magnoliae carbonyl reductase." XP002339862 Database accession no. AAH27641

D11: BREUER MICHAEL ET AL: "Industrial methods for the production of optically active intermediates." ANGEWANDTE CHEMIE (INTERNATIONAL ED. IN ENGLISH) 6 FEB 2004, Vol. 43, No. 7, 6 February 2004 (2004-02-06), pages 788-824, XP002339848 ISSN: 0570 0833

V.3 Novelty

D1 describes a method for producing 3-methylamino-1-(thien-2-yl)-propanol-1 wherein thiophene is reacted with 3-chloro-propionic acid chloride in the presence of a Lewis acid to form 1-(2-thienyl)-3-chloropropanone-1, and the propanone is reduced in the presence of an assymetrical transition metal catalyst and then reacted with methyl amine. This document does not, however, disclose the introduction of hydrogen halide.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D2 describes a method for producing 3-methy!amino-1-(thien-2-yl)-propanol-1, wherein 3-chlor-1-(thien-2-yl)-propanol is reacted with NaI to form 3-iodo-1-(thien-2-yl) propanol and is then reacted with methyl amine.

D3 describes the production of 3-chlor-1-(thien-2-yl)-propanol-1 by acetylating thiophene with chloracetyl chloride and reducing the ketone with sodium borohydride (figure 1).

D4 describes the production of 3-chlor-1-(thien-2-yl)-propanone-1 by carrying out a Friedel-Crafts reaction of thiophene with 3-chlorpropionyl chloride in the presence of tin tetrachloride as a Lewis acid catalyst with a 40% yield. The product is reduced, the chloride is reacted with NaI, and then reacted with methyl amine.

It should be noted that D5 describes the method of claim 1. 2M of hydrochloric acid are used rather than a hydrogen halide (example 1).

It should be noted that D6 describes a method for producing 3 methylamino-1-(thien-2-yl)-propanol-1 by reacting 3-chloro or 3 bromo-1-(thien-2-yl)-propanol-1 with methyl amine (examples 1 and 2).

D8 describes a nucleotide sequence and amino acid sequence of an R-specific alcohol dehydrogenase of *Lactobacillus brevis*. The amino acid sequence differs only at position 12 of SEQ ID No. 4 (isoleucine rather than valine).

None of the documents describes a method for producing 3-methylamino-1-(thien-2-yl)-propanol-1 like that in claims 1 and 21. Therefore, claims 1-10 and 21-26 meet the requirements of PCT Article 33(2).

None of the documents describes alcohol dehydrogenase like that in claim 11. Therefore, claims 11-15 meet the requirements of PCT Article 33(2).

Claim 16 describes a nucleic acid sequence comprising the coding sequence for the dehydrogenase according to one of claims 11 to 15 and is therefore novel.

Claim 17 describes an expression cassette comprising a nucleic acid sequence according to claim 15 and is therefore novel.

Claim 18 describes a recombinant vector comprising an expression cassette according to claim 16 and is therefore novel.

Claim 19 describes a prokaryotic or eukaryotic host with at least one vector according to claim 18 and is therefore novel.

Claim 20 describes the use of the dehydrogenase according to one of the claims 11 to 14 and is therefore novel.

V.4 Inventive step

Inventive step, claims 1-10 and 21-26: none of the cited documents renders obvious the introduction of hydrogen halide. The applicant shows on page 5, lines 14 ff. that the unwanted formation of the byproduct of formula II can be prevented. Therefore, claims 1-10 and 21-26 meet the requirements of PCT Article 33(3).

Inventive step, claims 11-20: in example 7 of the application, a cell suspension from the bacterial strain Lu10288, which was isolated by the inventors, was used to reduce a propanone, whereby the compounds (S)-3-methyl amino-1-(thien-2-yl)-propanol-1 are formed with an enantiomer excess of 95%. In example 8, a dehydrogenase was cloned from the same bacterial strain, resulting in SEQ ID No. 1 as an N-terminal sequence. The disclosure in D8 does not contain anything that would lead a person skilled in the art to recognize that the sequence motive according to alternative

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

a) in claim 11 could be characterized as a usable alcohol dehydrogenase. To the contrary, D8 actually leads away from the invention. Therefore, claims 11-20 involve an inventive step.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
DE 102 48 479 A			
DE 102 48 480 A			

BREUER MICHAELT ET AL: "Industrial methods for the production of optically active intermediates." ANGEWANDTE CHEMIE (INTERNATIONAL ED. IN ENGLISH) 6 FEB 2004, Vol. 43, No. 7, 6 February 2004 (2004-02-06), pages 788-824, XP002339848 ISSN: 0570-0833

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Clarity and support by the description (PCT Article 6):

1. Claim 11 b) relates to an alcohol dehydrogenase comprising at least 10 sequential amino acid residues according to SEQ ID No. 2 in the N-terminus area. It is doubtful, however, whether this SEQ ID No. 2 in fact involves the correct N-terminus of the alcohol dehydrogenase of *Candida magnoliae*. A sequence that differs from SEQ ID No. 2 is indicated as an N-terminus on page 48 of the description (example 10). Furthermore, **neither** of these N-terminal sequences corresponds to the partial amino acid sequence of the dehydrogenase represented by SEQ ID No. 6. Therefore, SEQ ID No. 2 as an N-terminus of the claimed alcohol dehydrogenase of *Candida magnoliae* is not sufficiently supported by the description.

2. Claim 16 relates to nucleic acid sequences that code for the dehydrogenases according to one of the claims 11-15 **or for derivatives thereof**. Since it is not specifically indicated that these are functionally equivalent derivatives, the claim lacks clarity (in principle, **every** nucleic acid sequence could be interpreted as being such a derivative, since **every** nucleic acid sequence can be derived from another nucleic acid through an undefined number of mutations, deletions and additions).

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/010939

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

The sequence listing in the description, pages 1-6, as originally filed.

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*